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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,324	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-9,11,15,22 and 41-51* is/are pending in the application.

4a) Of the above claim(s) *50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9,11,15,22 and 41-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page / 12/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on February 12, 2009.

Status of Claims

Cancellation of claims 2, 4, 10, 12-14, 16-21, and 23-40, amendment of claims 1, 3, 5-8, 11, 15 and 22, and addition of claims 41-51 is acknowledged.

Claims 1, 3, 5-9, 11, 15, 22 and 41-51 are currently pending and are the subject of this office action.

Claims 50 and 51 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Claim 50 recites rituximab as the second active agent, and claim 51 recites fludarabine as the second active agent, none of which corresponds to the elected species for the second active agent: hydroxyurea (see next).

Claims 1, 3, 5-9, 11, 15, 22 and 41-49 are presently under examination.

The following species are currently under examination: cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4yl}-amide as the selective cytokine inhibitory drug (from now on compound A), and hydroxyurea as the second active agent, which were elected in the reply filed on July 23, 2008.

Priority

The present application is a 371 of PCT/US03/11325 filed on 04/13/2003, and claims priority to provisional application No. 60/424,731 filed on 11/06/02.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (New Rejection Necessitated by Amendment)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 48 recites "wherein the compound is a solvate".

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention....one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

The term solvate, corresponds in some undefined way to specifically instantly disclosed chemicals. None of these meet the written description provision of USC 112, first paragraph, due to lack of chemical structural information for what they are since chemical structures are highly variant and encompass a myriad of possibilities. The specification does not appear to provide specific examples of any solvates, and while an implicit written description might exist for solvates of the drug with simple, widely known solvents such as water (i.e. hydrates) and methanol, no such description can be inferred for more complex solvents, e.g. t-butanol, polyols, etc.

Given the broad scope of the claimed subject matter, Applicant has not provided sufficient written description that would allow the skilled artisan to recognize all the solvates claimed.

Claim Rejections - 35 USC § 103 (Maintained rejection)

1) Claims 1, 5, 11, 15, 22 and new claims 41-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606).

The reasons for this rejection have been provided in the previous office action dated November 12, 2008, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicant respectfully submits the following:

(1) The cited references would not have provided any reason to combine their teachings so as to substitute Etanercept with isoindoline derivatives of Man et al., much less the instant compound, cyclopropanecarboxylic acid {2-[(1S)-l-(3-ethoxy-4-methoxy-phenyl)-2- methanesulfonyl-ethyl]-3-oxo-2,3-dihydro- 1H-isoindol-4-yl }-amide (compound A); and

(2) The cited references would not have provided the legally required reasonable expectation of success.

1. The cited references would not have provided any reason to combine their teachings so as to substitute Etanercept with isoindotine derivatives

The Examiner fails to establish the key novel and inventive elements of the instant claims: the administration of cyclopropanecarboxylic acid {2-[(1S)-l-(3-ethoxy-4-

methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro- 1H-isoindol-4-yl }-amide ("instant compound") for the treatment of specific MPD at the narrow dose range of from about 5 to about 50 mg per day. Indeed, while the instant claims narrowly focus on the administration of a specific compound for the treatment of specific MPD at a specific dose, the Examiner fails to establish that each of these claim limitations is taught or suggested in the prior art. See, e.g. In re Ochiai, 71 F.3d 1565, 1572. (Fed. Cir. 1995)) (PTO must establish "that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations.").

Further, the Examiner's rejection is flawed because it relies on the false assumption that there is a motivation to combine the teachings of Tsimberidou et al. and Man et al. so as to substitute Etanercept as taught by Tsimberidou et al. for the isoindoline derivatives taught by Man et al. Not only the cited references would not have provided any reason to combine their teachings for the treatment of myeloproliferative disease, but also the cited references have provided reasons as shown below not to combine their teachings so as to substitute Etanercept of Tsimberidou et al. with the isoindoline derivatives of Man et al., much less the instant compound.

Man et al. discloses in page 9, lines 18-28 that the isoindoline derivatives can be used to treat numerous possible disease states mediated by TNF-alpha, which, however, do not include polycythemia rubra vera (PRV), primary thromobocythemia (PT), and chronic myelogenous leukemia (CML), agnogenic myeloid metaplasia (AMM), or any other myeloproliferative disease (MPD). Man et al. further teaches that the invention of Man et al. "pertains to non-polypeptide", i.e., not a protein. See page 1,

lines 6-9 of Man et al. On the contrary, Tsimberidou et al. teaches a method of treating myeloproliferafive diseases with a protein, i.e., Etanercept (Enbrel; p75 TNFR:Fc), a protein comprising two naturally occurring soluble human 75-kilodalton TNF receptors linked to an Fe portion of an IgG1 (see Tsimberidou et al. at page 237, last paragraph), which clearly is not the small molecule compound recited in the currently amended claim 1. Further, Tsimberidou et al. at page 240, second full paragraph teaches that thalidomide, an isoindoline derivative, is not effective in patients with AMM. Therefore, the contradictory teachings of the cited references provide no motivation to combine so as to substitute Etanercept with the instant compound

Examiner's response: Tsimberidou teaches the treatment of the specific disease: Agnogenic Myeloid Metaplasia (AMM, one of the specific Myeloproliferative diseases listed in claim 1) with Etanercept (Enbrel, an inhibitor of the cytokine Tumor necrosis factor-alpha (TNF-alpha)). Tsimberidou also teaches that inhibition of TNF-alpha plays an important role in the treatment of several diseases including AMM (see abstract). In summary, Timberidou teaches that inhibition of TNF-alpha can be correlated with treatment of AMM. Man teaches that the instant claimed compound: {2-[(1S)-l-(3-ethoxy-4-methoxy-phenyl)-2- methanesulfonyl-ethyl]-3-oxo-2,3-dihydro- 1H-isoindol-4-yl }-arnide (Compound A) is a TNF-alpha inhibitor.

Since Tsimberidou teaches a method of treating AMM with a TNF-alpha inhibitor, and since Man teaches that compound A is a TNF-alpha inhibitor, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art

to substitute one functional equivalence (any TNF-alpha inhibitor) for another (compound A) with an expectation of success, since the prior art establishes that both function in similar manner, thus resulting in the practice of claims 1, 5, 11, 15 and 22, with a reasonable expectation of success.

Regarding the specific dose of compound A claimed (5 mg to about 50 mg per day, etc), Man further teaches that inhibition of TNF-alpha by these compounds can be conveniently assayed using methods known in the art (see page 20, lines 6-9). It further teaches that dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 1,000 mg/day as needed in single or multiple daily administrations. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF-alpha activity for other TNF-alpha mediated disease states by the compounds of the present invention (see page 22, lines 12-18). So, the skilled in the art, knowing the IC50 for compound A against TNF-alpha, and knowing the dosages recommended by Man (1 to about 1,000 mg/day) and the suggestion that the initial dosage can be copied from other TNF-alpha related diseases will be able to optimize the dose of compound A required to effectively treat AMM.

The fact that Man teaches that the isoindoline derivatives can be used to treat numerous possible disease states mediated by TNF-alpha, which, however, do not include polycythemia rubra vera (PRV), primary thromobocythemia (PT), and chronic myelogenous leukemia (CML), agnogenic myeloid metaplasia (AMM), or any other myeloproliferative disease (MPD) is irrelevant, because: first: Man also says on page 9

(lines 20-21) that the diseases include but are not restricted to the diseases listed; second: what it is important is that Man teaches that compound A is a TNF-alpha inhibitor, regardless of the use that Man is giving to this specific compound.

The argument that Man teaches inhibitors of TNF-alpha that are non-peptides, and Tsimberidou teaches a method of treating myeloproliferative diseases with a protein, i.e., Etanercept, which clearly is not a small molecule is also irrelevant. Tsimberidou, as mentioned before, clearly teaches that inhibitors of TNF-alpha in general are useful for treating AMM (see abstract), the fact that Timberidou teaches a protein as a TNF-alpha inhibitor does not mean that it teaches away from using small molecules as TNF-alpha inhibitors. There is nothing in the Timberidou reference that says or suggests that only peptide TNF-alpha inhibitors can be effective against AMM or that small molecule inhibitors of TNF-alpha will not be effective against AMM. As mentioned above: since Tsimberidou teaches a method of treating AMM with a TNF-alpha inhibitor, and since Man teaches that compound A is a TNF-alpha inhibitor, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any TNF-alpha inhibitor) for another (compound A) with an expectation of success, since the prior art establishes that both function in similar manner, thus resulting in the practice of claims 1, 5, 11, 15 and 22, with a reasonable expectation of success.

Regarding the statement by Applicant: "Further, Tsimberidou et al. at page 240, second full paragraph teaches that thalidomide, an isoindoline derivative, is not effective in patients with AMM", Examiner believes that Applicant has misinterpreted what

Tsimberidou says. Tsimberidou states: "Current treatment options other than: allogeneic stem call transplantation, including hydroxyurea, alpha-interferon, androgens, thalidomide, and splenectomy are ultimately ineffective in patients with AMM, and novel agents are required". By using the phrase "other than", the author means that the treatments cited afterwards do work against AMM, but nothing else seems to be effective against AMM.

Finally Man further teaches that the compounds of the invention can be in the form of salts (see page 12, lines 13-19), can be administered orally (see page 22, line 3),or in the form of tablets (see page 22, line 6).

2) Claims 3 and 7-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606) as applied to claims 1-2, 5, 10-11, 14-15 and 22-31 above, and further in view of Alter et. al. (Blood (1985) 66:373-379).

The reasons for this rejection have been provided in the previous office action dated November 12, 2008, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that claims 14-15 reciting the instant compound were not rejected in the previous office action

Examiner's response:, claims 14 and 15 were rejected in the Office Action mailed on November 12, 2008 (see page 10).

3) Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606) as applied to claims 1-2, 5, 10-11, 14-15 and 22-31 above, and further in view of Canepa et. al. (British Journal of Haematology (2001) 115:313-315).

The reasons for this rejection have been provided in the previous office action dated November 12, 2008, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that claims 14-15 reciting the instant compound were not rejected in the previous office action

Examiner's response: claims 14 and 15 were rejected in the Office Action mailed on November 12, 2008 (see page 10).

Claim Rejections - 35 USC § 103 (New Rejection Necessitated by Amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242) In view of Man et. al. (WO 2001/34606) as applied to claims 1, 5, 11, 15, 22 and new claims 41-47 above, and further in view of Vippagunta et. al. (Advanced Drug Delivery Reviews (2001) 48:3-26.

Claims 48 and 49 further limit claim 1, wherein the compound is a pharmaceutically acceptable solvate (hydrate in claim 49).

Tsimberidou and Man teach all the limitations of claims 48 and 49, except for the formation of an hydrate. However, Vippagunta teaches that formation of hydrates of known drugs is common practice in the pharmaceutical industry (see abstract).

At the time of the invention, it would have been *prima facie* obvious for the skilled in the art to further make a hydrate of compound A as taught by Vippagunta, thus resulting in the practice of claims 48- 49, with a reasonable expectation of success.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 112, first paragraph (scope of enablement).

Applicant's arguments have been fully considered and are persuasive.

Rejection under 35 USC 112, first paragraph (scope of enablement) is withdrawn.

Claims rejected under 35 USC 102 (a)

Due to Applicant's amendment of claim 1 the 102 rejection is now moot.

Rejection under 35 USC 102(a) is withdrawn.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
March 26, 2009

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612